SUPPORT FOR THE AMENDMENTS

Claims 1, 4, and 6 were previously canceled.

Claims 8, 18-20, 22-25, 27-30, and 32 are presently canceled.

Claim 9 is amended.

Support for the amendment of Claim 9 is provided by the specification at, for example, paragraphs [0020] – [0027].

The specification at paragraph [0023] has been amended to correct a clear typographical error. Support for the amendment can be found in paragraph [0009], paragraph [0026], the Examples, original Claim 1, original Claim 8, original Claim 9, and the Abstract.

No new matter has been added by the present amendments.

REMARKS

Claims 2, 3, 5, 7, 9-17, 21, 26, 31, and 33 are pending in the present application.

Applicants wish to thank Examiner Sutton for the helpful and courteous discussion with their undersigned Representative on June 7, 2011. During this discussion, various arguments (including those presented herein) were discussed. The content of this discussion is believed to be accurately reflected by the comments presented herein. Reconsideration of the outstanding rejections is requested in view of the amendments and remarks herein.

The rejections of:

(a) Claims 2, 3, 5, 7, 9, 12, 13, 26-29, 31, and 33 under 35 U.S.C. §103(a) over Usen et al (US 5,605,675) in view of Tomlinson et al (US 4,048,300) and Gates et al (US 5,882,630);

(b) Claims 14-17 and 21 under 35 U.S.C. §103(a) over Usen et al (US 5,605,675) in view of Tomlinson et al (US 4,048,300) and Gates et al (US 5,882,630) and further in view of Grabenstetter et al (US 4,083,955); and

(c) Claims 8, 10, 11, 18-20, 22-25, 30, and 32 under 35 U.S.C. §103(a) over Usen et al (US 5,605,675) in view of Tomlinson et al (US 4,048,300) and Gates et al (US 5,882,630)and further in view of Wiesel (US 6,287,120) and Grabenstetter et al (US 4,083,955),

are respectfully traversed.

Solely to expedite examination of the method as set forth in Claim 9, the claims related to the previously presented compositions of Claim 8 have been canceled. Applicants

submit that this cancellation is to be without prejudice and does not in any way indicate acquiescence to the Examiner's rejections.

In the outstanding Office Action the Examiner has modified the previous prior art rejections that appeared, most recently, in the Office Action mailed May 17, 2010, to add Gates (US 5,882,630).

Gates has been cited by the Examiner as disclosing that calcium glycerophosphate enhances the activity of ionic monofluorophosphates, such as sodium monofluorophsophate in oral compositions (see column 3, lines 10-28). As set forth on page 12 of the Office Action (see also page 14 of the Office Action), the disclosure by Gates is relied upon by the Examiner to support the allegation that the demonstrated results are not unexpected. Specifically, the Examiner relies upon Gates to support the position that "calcium glycerophosphate, which is disclosed by Ubsen et al. as a calcium ion source is used in conjunction with sodium monofluorophosphate, which is also disclosed by Ubsen et al., the activity of the monofluorophosphate is enhanced." Thus, the Examiner contends that the results demonstrated are expected from the method suggested by combining the cited art "due to the fluctuation of pH as taught by Tomlinson et al and due to the enhancement of the monofluorophosphate activity by combining the calcium glycerophophate as taught by Gates et al."

Applicants again submit that, unless the claimed invention is used as a guidepost, the art does not disclose alternately applying the separate compositions which are maintained discretely (Claim 8). Indeed, Usen et al fails to disclose alternately applying the separate compositions as claimed and also fail to disclose the pH of the separate compositions and/or the molar ratios in certain dependent claims.

Tomlinson et al discloses the alternate application of a composition, but merely describe monofluorophosphate as one of fluorides and is silent about calcium salts of polyol phosphate. Accordingly, the skilled artisan would not expect the claimed compositions Part A and B as claimed or alternately applying thereof to thereby maximum fluorine uptake. Further, Tomlinson fails to disclose the molar ratios in certain dependent claims.

The Examiner disregards all of these deficiencies and maintains that the alternate application of the claimed compositions Part A and B and the results flowing therefrom are obvious and/or expected. The Examiner further maintains that irrespective of their individual deficiencies the claimed method would be obvious. Applicants disagree with this position by the Examiner.

Tomlinson discloses dental preparations containing fluorapatite, fluorohydroxyapatite and hydroxyapatite (see abstract). The Examiner stated "Tomlinson teaches a composition comprising a first component comprised of fluoride and orthophosphoric acid with a pH of about 3 to 4; and a second component comprised of a calcium salt having a pH of about 7." The Examiner indicates that Tomlinson teaches a method of alternately applying the compositions in Example 12. However, Tomlinson clearly indicates that the second component have therein solid synthetic Brushite residue.

In other words, Tomlinson's composition comprises the first component comprised of sodium fluoride and orthophosphoric acid; and the second component comprised of A) calcium nitrate and B) phosphoric acids (sodium monohydric orthophosphate and sodium dihydric orthophosphate) to thereby produce the solid Brushite residue in the second component.

In contrast, Usen discloses a composition comprising which is present in two phases: A) one phase contains calcium compound and B) the other contains inorganic phosphate and fluorine compound (e.g., sodium fluoride) (see, abstract).

As discussed above, Tomlinson discloses that A) calcium nitrate (calcium source) and B) phosphoric acids in the second component are mixed before applied to teeth, which corresponds to Usen's composition comprising calcium compound as one phase (A mentioned above) and phosphate and fluoride compound as the other phase (B mentioned above). That is, both of Tomlinson and Usen disclose that calcium salt (calcium source) and phosphate are mixed before being applied to teeth. Accordingly, neither of these references disclose or a calcium compound which is calcium source and phosphate which is fluoride ion source are *alternately* applied to teeth.

Tomlinson merely discloses that the first component and second component comprising solid Brushite (calcium phosphate, $CaHPO_4 \cdot 2H_2O$) are alternately applied to teeth. Tomlinson differs from the claimed invention in the components to be alternately applied to teeth. The second component of Tomlinson is a solution fur applying solid Brushite (calcium phosphate) to teeth, which is also different from the second phase of Usen. Accordingly, alternate application of two components disclosed by Tomlinson could not have been combined with the teach of Usen since the two components to be alternately applied are different between these references.

Usen discloses that the A) calcium component (calcium source) and B) phosphate and sodium fluoride are mixed each other immediately before applied to teeth, to thereby form calcium phosphate on the surface of teeth, which is a co-mineralization technique utilizing chemical reaction. In contrast, Tomlinson discloses that solid Bushite (calcium phosphate), the second component, is applied to teeth, which is a technique to bring Brushite to teeth

utilizing physical action. Thus, Usen's technique utilizing chemical reaction is completely different from the technique in Tomlinson utilizing a physical action. Thus, Tomlinson and Usen are not combinable at all to arrive at the claimed invention.

Moreover, the skilled artisan would not have expected the benefits of the claimed invention based on their combined disclosures. Indeed, according to Tomlinson, the pH of the second solution is adjusted to 7 after making Brushite, which is believed to quit allowing Brushite to be dissolved in the solution. Therefore, Tomlinson's disclosed technique is different from the claimed invention in the purpose and effect of adjusting the pH of the solution.

To underscore the foregoing, the Examiner is invited to look at the specific details of Tomlinson which clearly show that this disclosure only discloses separate application when the material being applied is Brushite. During the discussion with the undersigned, the Examiner emphasized that Tomlinson is not limited to this example. The Examiner also expressed the opinion that Tomlinson sufficiently discloses a method of alternately applying the composition to the teeth that is not restricted to a second composition in which Brushite has formed. To support this position, the Examiner pointed to column 8, lines 47-68, column 9, lines 1-13, and column 9, lines 28-38.

Although Applicants agree that Tomlinson is not limited to its examples, Applicants dispute the Examiner's conclusions based on Tomlinson. Specifically, in each of the aforementioned sections Tomlinson specifically requires the calcium component to be present with orthophosphates, which *will* form Brushite. Accordingly, Example 12 is representative of Tomlinson as a whole and when these additional reasons are coupled with the arguments already of record (see remarks set forth in the response filed October 29, 2010, which are incorporated herein by reference) the claimed invention would not be obvious.

Nonetheless, to expedite allowance of this application, Applicants have amended Claim 9 to be commensurate in scope with the evidence provided, for example, by adding concentration limitations and defining the components. Specifically, Claim 9 now recites:

> A method of treating teeth, comprising alternately applying a first composition (A) and a second composition (B) to a tooth:
>
> (A) a first composition containing an inorganic fluoride and an inorganic phosphoric acid or a salt thereof, wherein an aqueous solution of said first composition has a pH value ranging from 2 to 6 wherein the molar ratio of said inorganic fluoride to said inorganic phosphoric acid or salt thereof falls in the range of 0.1 to 10 wherein the content of said inorganic fluoride ranges from 0.025 mol/l to 0.5 mol/l and the content of said inorganic phosphoric acid or a salt thereof ranges from 0.05 mol/l to 1 mol/l wherein said inorganic fluoride is selected from the group consisting of sodium fluoride and ammonium fluoride and said inorganic phosphoric acid or a salt thereof is orthophosphoric acid or a metal salt thereof; and
>
> (B) a second composition containing a monofluorophosphate and a calcium salt of polyol phosphate, wherein an organic acid constituting the calcium salt of organic acid has a pKa value ranging from 3 to 11, or at least one pKa value ranging from 3 to 11 when the organic acid has plural pKa values wherein an aqueous solution of said second composition has a pH value ranging from 6 to 12 wherein the content of said calcium salt of polyol phosphate ranges from 0.02 to 0.5 mol/l and the content of said monofluorophosphate from 0.05 to 5 wt% wherein said calcium salt of polyol phosphate is selected from the group consisting of calcium glycerophosphate and calcium glucose-l-phosphate.

With the amendment above, Applicants submit that the claims contain yet another distinction over the disclosures of Tomlinson and Usen. Specifically, in amended Claim 9, the calcium salt of polyol phosphate in the second composition is selected from the group consisting of calcium glycerophosphate and calcium glucose-l-phosphate. Tomlinson and Usen, at best, disclose that calcium nitrate, calcium sulfute or the like are used in their examples. This difference is important as the evidence of record clearly shows that calcium glycerophophate or calcium glucose-l-phopbate provide a remarkable result when alternatively applying the two compositions as compared to the applying the mixture of two compositions which have been mixed immediately before being applied.

Applicants again remind the Examiner that "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)" Thus, the experimental data presented in the Declarations filed on October 29, 2010 and Janaury 25, 2010, as well as the previously filed Yamagishi Declarations filed on February 26, 2009 and January 25, 2010, clearly illustrates that substantial benefits flowing from the claimed method, which are enough to rebut a *prima facie* case of obviousness.

Again, with respect to the experimental data of record, which is fully representative of the claims as currently presented, in paragraphs 10-17 of the Declarations a comparison was provided of a single composition (i.e., mixed application), which reflects the disclosure of Usen et al, to the presently claimed alternate application. Illustrated in Table 4 is that the composition of the claimed invention provides a significant improvement in the fluorine uptake and HAP surface. Also provided in these Declarations was clear evidence of the importance of a second composition containing a monofluorophosphate and a calcium salt of polyol phosphate wherein an aqueous solution of said second composition has a pH value ranging from 6 to 12. Indeed, the criticality of this combination is provided by the data in Table 4, as well as the detailed experiments in paragraphs 14-17. In paragraph 17, it is clearly summarized that a mixed solution having a low pH in due to the presence of calcium nitrate or calcium lactate would not be suitable for repairing teeth would not be repaired, but rather would melt teeth. Neither Usen et al nor Tomlinson et al specifically disclose or exemplify a second composition containing a monofluorophosphate and a calcium salt of

polyol phosphate wherein an aqueous solution of said second composition has a pH value ranging from 6 to 12, much less disclose or suggest this result.

To further illustrate the differences between the claimed invention and the cited art, the Declaration of October 29, 2010, further provided new paragraphs 18-20 to further illustrate the unexpected results flowing from the claimed invention.

Tomlinson et al merely describe monofluorophosphate as one of the fluorides and is silent about calcium salts of polyol phosphate, specifically those of the present claims. This deficieny is significant as a critical distinction giving rise to an unexpected result is in the specific alternately application of a first composition (A) and a second composition (B) to a tooth in accordance with the pending claims.

Indeed, as stated above, in the Example 12 of Tomlinson et al calcium nitrate is used. When calcium nitrate was used for the substitution of calcium glycerophosphate, the surface of HAP was melted. These results are shown in Table 3 and 4 of the Declaration submitted October 29, 2010 (see Comparative Examples C1 and C2). Further, in paragraph 18 of the Declaration submitted October 29, 2010 Applicants provide Figures 2-1 through 2-3, which illustrate the effects of the Comparative Example 1 in relation to the Example of the present application.

In Figure 2-1, shows HAP powder before treatment. columnar crystals of HAP are observed before HAP powder treatment. Figure 2-2 shows HAP powder after treatment by the composition identified as Comparative Example C1 in Table 3 above. Columnar crystals of HAP are melted. This result shows that HAP is melted when Comparative Example C1 is applied by alternative treatment. In Table 4 above, fluoride uptake of Comparative Examples C1 and C2 are 8.25 and 6.21, respectively. These values look higher than the example of the claimed invention at first glance. However, this does not tell the complete story as HAP was

melted and the calcium ion is released from HAP. The calcium ion is combined with fluoride and becomes calcium fluoride on the surface of HAP. Calcium fluoride is easily dissolved in saliva and, as a result, calcium fluoride in the saliva was detected for fluoride uptake.

Figure 2-3 shows HAP powder after treatment by the composition identified as Example in Table 3 above. It is observed that columnar crystal of HAP was not melted and many small crystals were attached on the surface of HAP. These small crystals contain "calcium fluoride", "hydroxyapatite", and "calcium phosphate". When calcium fluoride coexists with hydroxyapatite and/or calcium phosphate, calcium fluoride is hardly dissolved into saliva and fluoride is taken into HAP. The fluoride taken into HAP forms into FHAP ($Ca_{10}(PO_4)_6F_2$).

From the foregoing, it is shown that Comparative Examples C1 and C2, which contain calcium nitrate is substantially inferior to the Example if the presently claimed invention containing calcium glycerophosphate. As stated in paragraph 18 of the Declaration submitted herewith, when this evidence is taken together with the data in Table 4 the criticality in using calcium glycerophosphate is clearly demonstrated, which represents and unexpected result in view of the cited art.

Moreover, in paragraph 19 of the Declaration submitted October 29, 2010, Applicants provide Tables 6 and 7 (below) showing the solubility and concentration in saliva:

Table 6

	Solubility
Calcium fluoride	18 mg/l
Hydroxyapatite	1 to 3 mg/l
Calcium hydrogen phosphate	200 mg/l

Table 7

	concentration in saliva
Calcium	20 to 30 mg/l
Fluoride	0.03 mg/l
Phosphate	200 to 300 mg/l

Since the concentration of fluoride in saliva is low, calcium fluoride is easily dissolved into saliva. In contrast, because concentration of phosphate in saliva is high, calcium hydrogen phosphate is hardly dissolved into saliva. Therefore, calcium fluoride must coexist with hydroxyapatite and/or calcium phosphate for re-calcification (re-mineralization). Figures 3-1 and 3-2 in the Declaration submitted October 29, 2010 provided an illustration of the scheme to provide a better understanding.

Thus, it is summarized in paragraph 20 of the Declaration submitted October 29, 2010 that the alternative treatment with two compositions as claimed, an unexpected result was obtained when the composition contains a calcium polyol phosphate (such as calcium glycerophosphate). Since Tomlinson does not disclose calcium polyol phosphate and Usen et al do not disclose alternative treatment, claimed method is not obvious. Moreover, the claimed invention provides an unexpected result when considering the additional disclosures of US 4,083,955 (Grabenstetter) and US 6,287,120 (Wiesel).

Thus, the data of record clearly rebut even a *prima facie* case of obviousness.

Withdrawal of these grounds of rejection is requested.

The rejection of Claims 2, 3, 5, and 7-33 under 35 U.S.C. §112, second paragraph, is obviated by amendment. Applicants submit that the claims as presented herein are free from the antecedent basis criticism raised by the Examiner. Withdrawal of this ground of rejection is requested.

Applicants submit that the present application is now in condition for allowance.

Early notification of such action is earnestly solicited.

Respectfully submitted,

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